

1 **Modeling PRRSV-2 prevalence within a farrowing room**

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5 **ABSTRACT**

6

7 **Introduction**

8 Porcine respiratory and reproductive syndrome virus (PRRSV) poses a significant challenge to
9 the global swine industry (Calderón Díaz et al., 2020; Holtkamp et al., 2013). Ascertaining the
10 PRRSV status of pig populations around the time of weaning is crucial to guide decisions on
11 health interventions and pig flow (Holtkamp et al., 2011).

12
13 Efficient PRRSV surveillance/monitoring programs allow for the early detection of infection
14 and helps evaluate changes in PRRSV prevalence over time; aiding swine producers and
15 veterinarians alike to forestall the spread of a PRRSV (Mccaw, 2000; Silva et al., 2017), and
16 evaluate progress made with instituted PRRSV management programs (Holtkamp et al., 2021;
17 Linhares et al., 2014).

18
19 Different sample types are routinely submitted to Veterinary Diagnostic Laboratories in the US
20 for PRRSV investigation by RT-rtPCR; these would include samples taken from individual pigs
21 such as serum, swabs, semen, and post-mortem tissues; or aggregate samples taken from multiple
22 pigs such as processing fluids and oral fluids (Trevisan et al., 2019). These samples are either
23 submitted and tested individually or in pools.

24
25 The number of samples submitted for disease pathogen investigation is crucial to the success of a
26 surveillance/monitoring exercise. Guided by some epidemiological assumptions, the sample size

should have enough power to detect at least one positive unit if the herd is truly positive for the pathogen of interest (Cameron et al., 2020; Stevenson, 2021).

Estimated prevalence at the individual pig level is one of the key variables used in calculating sample size to demonstrate disease freedom (Fosgate, 2009; Stevenson, 2021).

The reference sample for PRRSV surveillance in sow herds is serum from weaning-age pigs (Holtkamp et al., 2011). Although the serum sample is the sample of choice for PRRSV surveillance, it requires more skill, more manpower, is less animal welfare friendly, and is often impractical for frequent PRRSV surveillance in large herds (Turlewicz-Podbielska et al., 2020) compared to other (alternative) sampling options. For this reason, since 2018, aggregate alternative samples have been the most frequently submitted samples for PRRSV surveillance in the US (Trevisan et al., 2019).

Almeida (Nunes de Almeida, 2020) demonstrated that, especially in low prevalence, Family oral fluids (FOFs) are a more convenient and cost-efficient alternative to serum sampling for PRRSV surveillance in weaning-age pigs. A FOF sample is an aggregate sample obtained when oral fluids are wrung off a rope chewed by a sow and her piglets (Almeida et al., 2020). A challenge with interpreting a positive result from testing aggregate sample types is that one only knows that at least one animal that contributed to the sample matrix is pathogen-positive (shedding) but cannot ascertain how many animals exactly are shedding.

Consequently, little to nothing is known about the number of positive pigs in a sampled room given the proportion of test-positive aggregate samples, such as FOF, obtained from that room.

The individual pig is the unit for which sample size is calculated when non-aggregate samples are collected, while the litter is the unit for which sample size is calculated when an aggregate sample such as FOF is to be collected (Rotolo et al., 2017)(Osemeke et al., 2022, *unpublished*); it will be helpful to swine practitioners in making sampling decisions if they understood how the proportion of PRRSV-positive piglets related with the proportion of PRRSV-positive litters, as both parameters are needed assumptions in estimating sample sizes.

To the best of our knowledge, the relationship between the mentioned proportions in a swine farrowing room has not been previously characterized. This study builds upon a previous study

that assess the observed probability of a positive FOF sample given the number of viremic (PRRSV-positive) pigs within a litter (Almeida, Zhang, Lopez, et al., 2021), celled apparent litter prevalence (ALP). We further develop an *in silico* study to assess the true litter prevalence (TLP) and finally to model a relationship between the ALP and TLP in a farrowing room. It is expected that the results from this study will not only provide insights to swine practitioners as to the likely relationship between PP, TLP, and ALP, but also provide a template/framework for determining piglet-level prevalence of PRRSV (and potentially other swine pathogens) that are being monitored using aggregate samples.

2. Methodology

2.1 PRRSV detection in pig litters using FOF

Based on a dataset from Almeida et al. (Almeida, Zhang, Zimmerman, et al., 2021) 199 litters had all piglets sampled for PRRSV RNA detection by RT-rtPCR (reverse transcription, real time polymerase chain reaction); also, each i litter was sampled using FOF. The litters were sampled from 11 farrowing rooms across 6 different swine breeding farms.

The effect of the proportion of positive piglets (x) on the detection of a positive litter using FOF (P^{FOF}) was assessed with a generalized linear mixed model employing a logit link function and a 'residual' Bernoulli distribution. In addition, the linear predictor comprised random effects for farms (j) according to:

$$\text{logit}(P_{ij}^{FOF}) = \alpha + \beta x_{ij} + \varepsilon_i + \gamma_j, \quad (1)$$

where α is the intercept of the model. ε_i is the random error assumed $\varepsilon_i \sim N(0, \sigma_\varepsilon)$, and γ_j is the random effect accounting for the farm-effect in the model, assumed $\gamma_j \sim N(0, \sigma_\gamma)$, where $\varepsilon_i \perp \gamma_j$.

Approximate maximum likelihood inference was based upon Laplacian integration, as implemented in R (R Core Team, 2018) in routine glmer from library lme4 (Bates et al., 2015).

2.2 Stochastic model

Let's consider a random variable: number of positive piglets in the i -th litter (N_i), assuming that each piglet's status (positive/negative) is a Bernoulli trial, with a fixed p probability, thus N_i arises from a binomial process. Consider a room with n litters with different sizes (T_i) drawn from a discrete empirical distribution, and total number of piglets in the room $T = \sum_{i=1}^n T_i$. In a simplistic scenario, the allocation of positive piglets in each litter (N_i) would follow the relative

size of the litter in the room. However, given that we are modeling an infectious disease, there might be a situation where the total number of positive animals (N) may be "clustered" in a few litters.

Accounting for this, the number of positive animals in each i litter (N_i) is calculated as a special case of the multinomial distribution, sampling recursively from binomial distributions using a clustering factor:

$$N_i | N_j (j = 1, \dots, i-1) \sim \min \{ \text{Bin}[(N - \sum_{j=1}^{i-1} N_j, pl_i)], T_i \}, \quad (2)$$

where j stands for the successive allocation of positive animals within each litter. pl is the probability of success in this binomial process. Finally, pl is defined as:

$$pl_i = \frac{T_i}{T - \sum_{j=1}^{i-1} T_j} + \left(1 - \frac{T_i}{T - \sum_{j=1}^{i-1} T_j} \right) * c, \quad c \in [0,1]. \quad (3)$$

The reader should be aware that c is a clustering factor. Thus when $\lim_{c \rightarrow 1} pl = 1$, and the positive piglets will be totally clustered in the smallest number of litters as possible. On the other hand, when $\lim_{c \rightarrow 0} pl = \frac{T_i}{T - \sum_{j=1}^{i-1} T_j}$, piglets will be spread according to the relative size (number of piglets) of each litter regarding the room size.

To obtain the clustering factor c we used the observed distribution of the within litter prevalence (θ_i) reported in Almeida et al. (Almeida, Zhang, Zimmerman, et al., 2021) across seven rooms, each room with n litters. The lost function was the minimization of the mean squared errors of the predicted (eq 2) vs observed distribution of the within litter prevalence $f(c, \theta) = \frac{1}{n} \sum_{i=1}^n (\theta_i - \frac{N_i}{T_i})^2$. The objective function $f(c, \theta)$ can be used to calculate a parameter estimate $\hat{c} = \text{argmin}(f(c, \theta))$. Each room was randomly chosen, 5000 times obtaining the parameters θ_i , N_i , and T_i . For each sampled room, 300 values of c were sampled from a uniform distribution $c \sim \text{uniform}(0, 1)$, obtaining a distribution to optimize \hat{c} .

2.2.2 Apparent prevalence at the litter level

The simulated proportion of positive piglets per litter obtained from 2.2 were used as input for the logistic model fit in 2.1, calculating the marginal probability of detection of each simulated litter using FOF sampling. Now we are interested in modeling a random variable (S) describing the

number of positive litters detected in a routine FOF sampling in a farrowing room. Assuming the probability of each litter being detected by FOF (P_i^{FOF} see eq. 1) are independent of each other, and the positive/negative status of a litter $y_i \sim \text{Bernoulli}(P_i^{FOF})$, S equals $\sum_{i=1}^k y_i$. The parameters and distributions used in the simulations are described in table 1. In this simulation, 5000 stochastic iterations were performed, each one representing a different room, propagating the between litter variability observable in different farrowing rooms.

Table 1 – Descriptions of model parameters used to compare the true and apparent liter prevalence of PRRSV.

Parameter/variable	Distribution/function	Description	Source
P	Fixed= (range of values from 1% to 100%)	Probability of a piglet being positive in a room (prevalence)	Almeida
N	$p*T$	Total number of positive animals in the room	Calculation
T	$\sum_{i=1}^n T_i$	Total number of piglets in the room	Calculation
T_i	empirical $\{(), ()\} *$	Number of piglets in the i -th litter	Almeida
N	Fixed=56	Number of crates in a room	Almeida
N_i	$\min \left\{ \text{Bin} \left[\left(N - \sum_{j=1}^{j=i-1} N_j, pl \right) \right], T_i \right\}$	Number of positive piglets in i -th litter	Calculation
pl_i	$\frac{T_i}{T - \sum_{j=1}^{j=i-1} T_j} + \left(1 - \frac{T_i}{T - \sum_{j=1}^{j=i-1} T_j} \right) * c$	Probability of success in this binomial process (i.e., allocation of positive piglets in a litter) for the in i -th litter	Calculation
C	Fixed=0.63	Clustering factor	Optimized based on Almeida

* empirical $\{(3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 25), (0.0092, 0.0092, 0.0046, 0.0046, 0.0553, 0.0691, 0.0922, 0.1014, 0.1982, 0.2074, 0.1244, 0.0783, 0.0415, 0.0046)\}$

2.3 Sensitivity analysis

To assess the effect of the clustering factor (c) and the room size (n) on the estimated relationship between pig-level-prevalence and litter-level prevalence we selected five values for c (0.05, 0.34, 0.63, 0.83, 1) and five values for n (10, 33, 56, 79, 102) combining then as a factorial design for the sensitivity analysis, totaling 25 different scenarios.

3. Results

3.1 PRRSV detection in pig litters using FOF

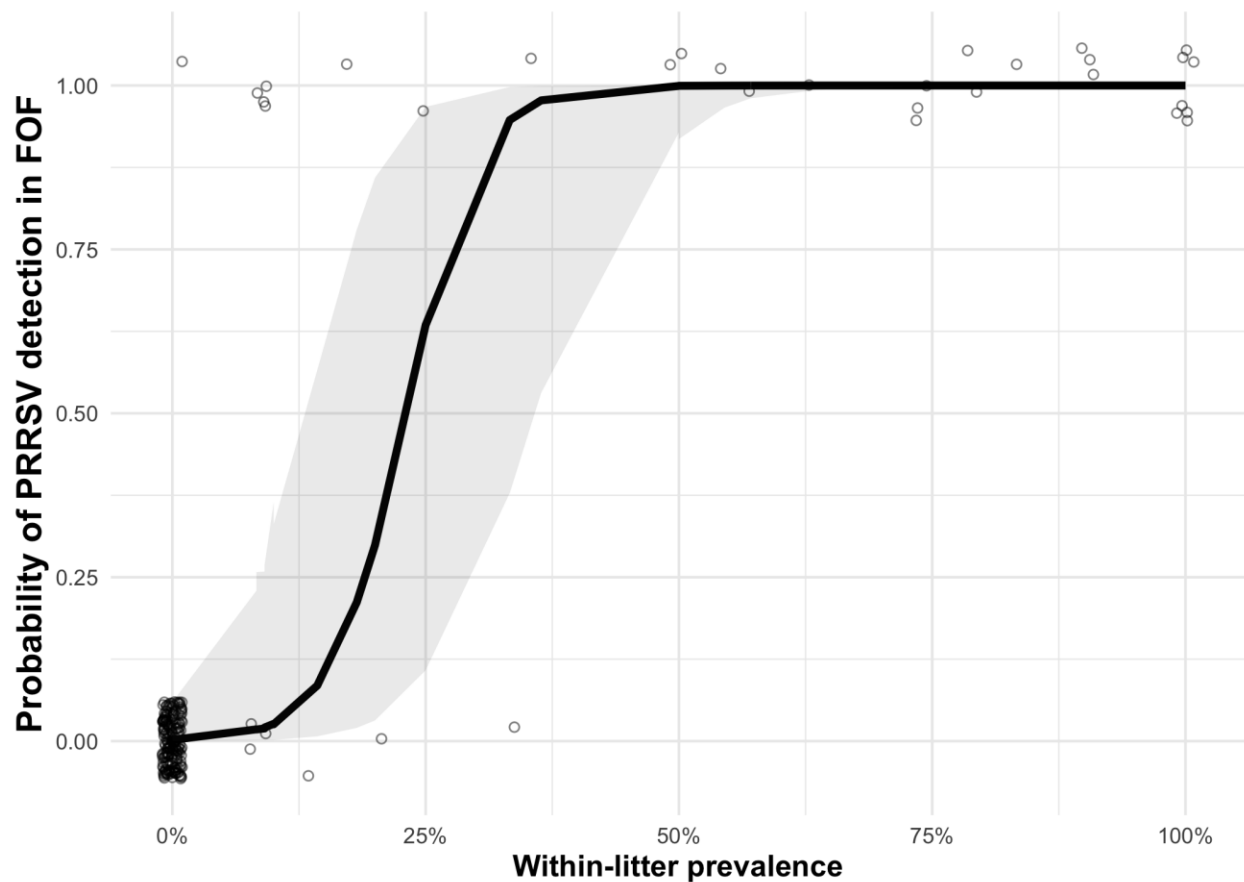


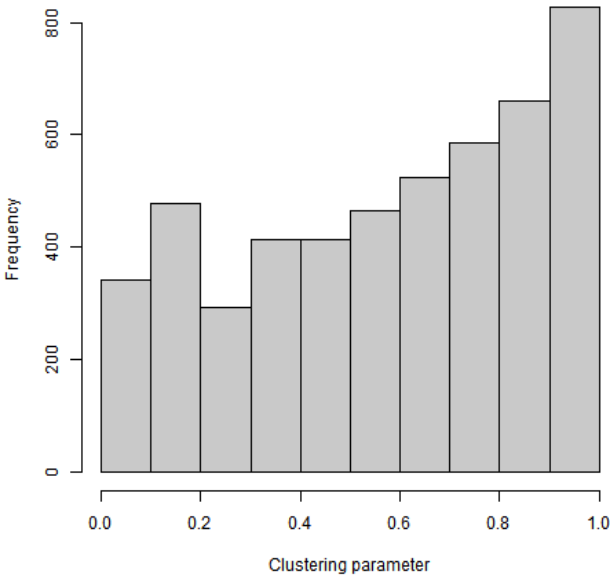
Figure 1: Probability of PRRSV detection in FOF for different within litters prevalence. Dots are the observed PRRSV detection by PCR, and 95% prediction intervals are represented by the grey region around the regression line.

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140 **3.2 Stochastic model**

141 **3.2.1 Observed distribution of clustering in sampled farms**

142 The clustering distribution across all sampled rooms had a minimum value of 0, a median of
143 0.629, a mean of 0.580, and a maximum value of 1. The distributions of the clustering parameter
144 across all sampled rooms are represented in figure 2



145

146 Figure 2: Distribution of the clustering parameter c obtained by the optimization of the predicted and
147 observed within litter prevalence across all sampled rooms from Almeida's study.

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149 **3.2.2 The relationship between piglet-level prevalence and litter-level prevalence**

150 Table 2: Relationship between the proportion of positive piglets in a 56-crate farrowing room and
151 the True and Apparent (by FOF) proportion of positive litters assuming a clustering level of 0.63.

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Proportion of PRRSV-positive piglets	True proportion of PRRSV-positive litters (Upper and lower 95% quantiles)	Apparent proportion of PRRSV-positive litters by FOF
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(%)	(%)	(Upper and lower 95% quantiles) (%)
1	3.57(1.79,7.14)	1.79(0.00,3.57)
5	8.93(5.36,10.71)	7.14(5.36,8.93)
10	14.29(10.71,16.07)	10.71(8.93,14.29)
15	17.86(16.07,21.43)	16.07(14.29,19.64)
20	23.21(19.64,26.79)	21.43(17.86,25.00)
25	28.57(25.00,32.14)	26.79(23.21,30.36)
30	33.93(30.36,37.50)	32.14(28.57,33.93)
35	39.29(35.71,42.86)	35.71(33.93,39.29)
40	42.86(39.29,48.21)	41.07(37.50,44.64)
45	48.21(44.64,51.79)	46.43(42.86,50.00)
50	53.57(50.00,57.14)	51.79(48.21,55.36)

Figure 3: A plot of litter prevalence against piglet level prevalence for a 56-crate farrowing room, assuming a clustering level of 0.63.

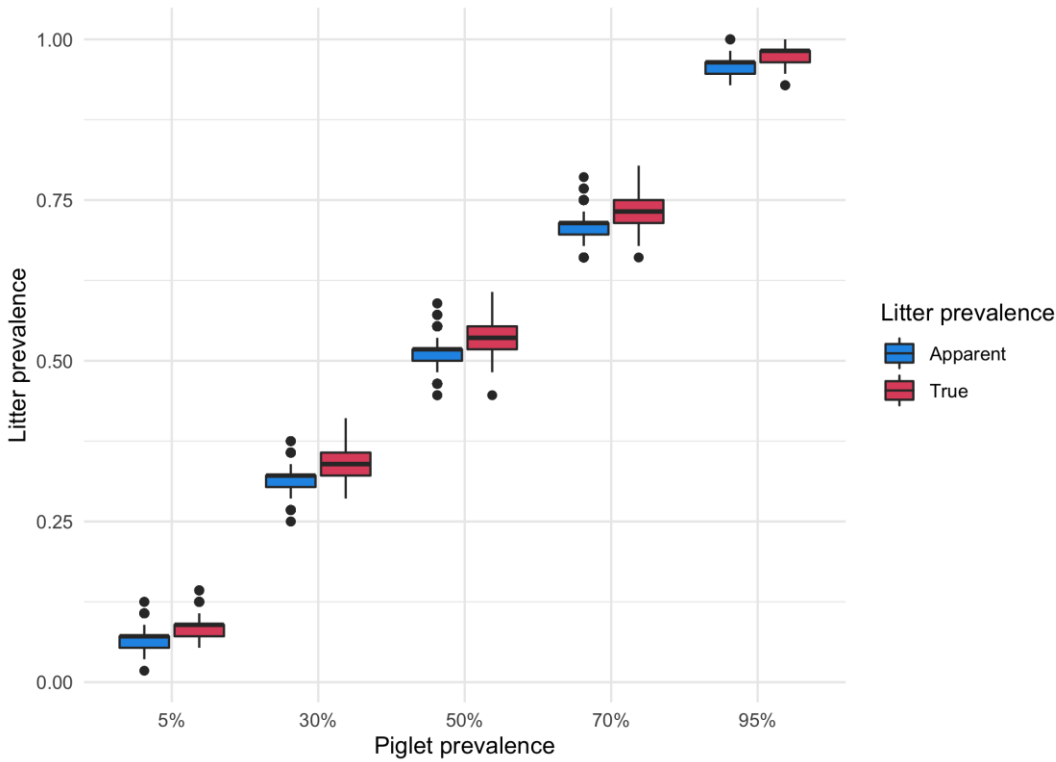


Figure 3: Distribution of true-and apparent litter prevalence in a 56-crate room given different piglet-level prevalence scenarios and a clustering factor of 0.63.

3.3 Sensitivity analysis

The sensitivity analysis was done to evaluate the effect of variations in clustering level and room size on the proposed relationship between piglet level prevalence and litter prevalence. As can be seen from the plots, ALP was relatively more stable to changes in clustering and number of crates compared to TLP. Generally, TLP and ALP increasingly converged to similar values with increasing clustering and increasing room size. Clustering changes appeared to have a more significant effect on ALP and TLP than changes in the number of crates in the room.

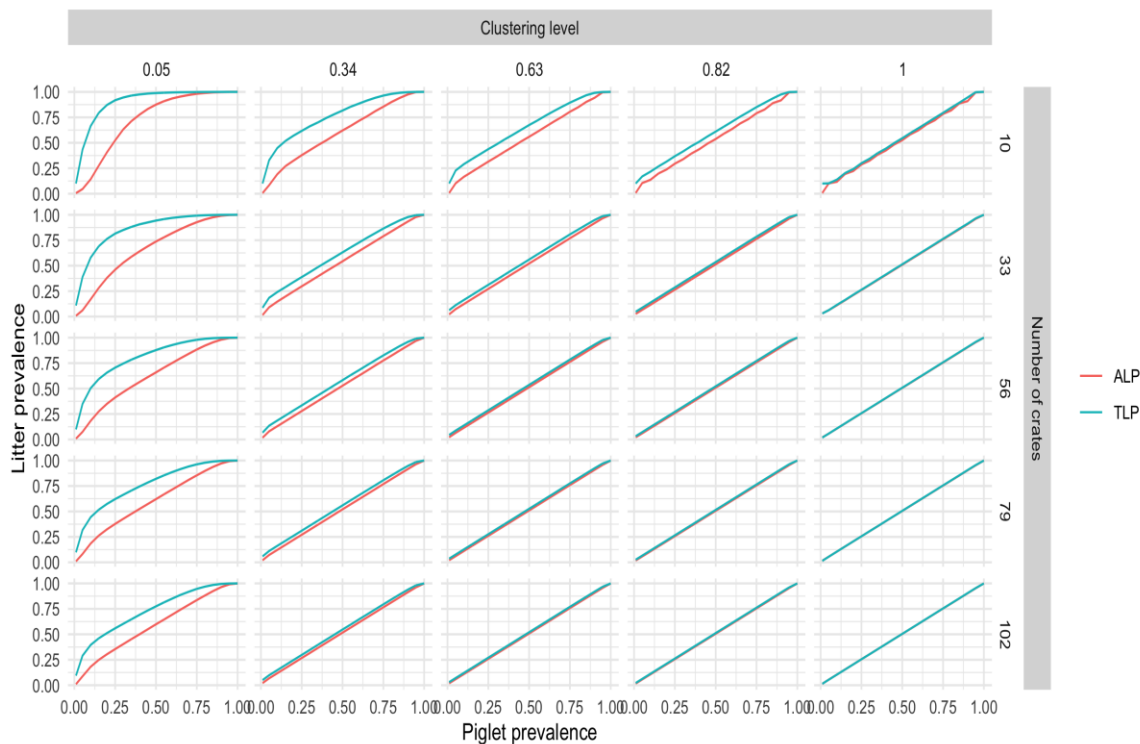


Figure 4: Changes in the relationship between the proportion of PRRSV-positive pigs and the proportion of PRRSV-positive litters (True and Apparent) with changes in clustering of PRRSV within room, and number of litters within rooms.

4. Discussion

The use of mathematical models to describe disease dynamics in swine populations is not new. Mathematical models have been used to characterize and describe PRRSV transmission dynamics (Amirpour Haredasht et al., 2017; Evans et al., 2010; Nodelijk et al., 2000; Phoo-ngurn et al., 2019; Rotolo et al., 2017; Suksamran et al., 2017) and to also evaluate PRRSV control strategies (Arruda et al., 2016; Jeong et al., 2014).

Perhaps explained by the theory of PRRSV being highly infectious but not highly contagious (Pileri & Mateu, 2016), or by the mere fact that pigs in conventional US barns do not interact randomly with each other (ref) and are more likely to transmit PRRSV to pigs within the same crate or with their closest neighbors (Murato et al., 2020), some studies have described the non-homogenous distribution of PRRSV in pig barns (M. N. Almeida et al., 2021; Rotolo et al., 2017)

Clustering estimates the degree of homogeneity (or more aptly put; heterogeneity) of PRRSV between litters in a farrowing room; it may be overreaching to deterministically model a one-size-fits-all clustering for PRRSV. This is because the spread of PRRSV between litters within a farrowing room would depend on 1) Management practices such as cross-fostering, and vaccination (Mccaw, 2000; Pileri & Mateu, 2016) 2) PRRSV strain (there is evidence of differences in characteristics such as virulence and spread between PRRSV strains) (Cho et al., 2007; Ogno et al., 2019; Pileri & Mateu, 2016) 3) Barn structure (for example, presence or type of ventilation systems in use) (ref) 4) Time since outbreak 5) Secondary infections which may increase pig susceptibility to PRRSV, encourage huddling or increase production of infectious respiratory fluids(ref). This uncertainty however does not undermine the importance of these results, on the contrary, it adds some precision to the list of conventional epidemiological assumptions guiding sample size calculations for disease pathogen surveillance viz a viz making an informed guestimate of the clustering level in addition to disease prevalence.

Paper on R0 of PRRSV and role of vac and biosec (Pileri & Mateu, 2016)

A critical goal of this study is to estimate the most likely relationship between the pig level prevalence and apparent litter prevalence by FOF, considering the pen-level sensitivity and specificity of this sample type. As observed from Figure 3, ALP is not as sensitive as TLP to variations in clustering parameter; we are therefore confident of the estimates on Table 2.

One can also decide the number of crates to randomly sample for FOF to detect a disease given an assumed pig level prevalence. For example, assuming an at least 10% pig-level prevalence, serum sampling requires you sample about 30 pigs to be 95% confident of detecting at least one positive animal (Cannon & Roe, 1982; Holtkamp et al., 2011). From the table, 10% pig-level prevalence corresponds to about 11% ALP or about 7 litters in a 56-crate room likely to give a positive FOF test. This number can be used to calculate an appropriate sample size for FOF to detect at least 1 positive litter; Table 2 is therefore useful to the practitioner in tying back what an assumed litter prevalence would mean at the individual pig level.

Another key application of the proposed tables is to help the practitioner estimate his piglet-level prevalence given the results of FOF-testing. Given that a representative number of litters were sampled (sample size to estimate prevalence), the proportion of positive FOF results on RT-qPCR tests (apparent litter prevalence by FOF) can be used to deduce the likely proportion of total pigs that are PRRSV-positive pigs (piglet-level prevalence).

5. Conclusion

This study explored the use of mathematical models to characterize the relationship between PP, TLP, and ALP in a farrowing room. A key takeaway from this study is the demonstration of the effect of a clustering parameter on the characterized relationship between the mentioned proportions; like other sampling assumptions, clustering could be considered when estimating probable sample size.....

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